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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,062	02/21/2002	John David Charles Rosamund	056291-5073	8999

9629 7590 02/08/2005

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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,062	ROSAMUND ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/19/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10 and 15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10 and 15-23* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/19/04 has been entered.

2. Applicant's amendment filed on 11/19/04 is acknowledged.

Status of Claims

3. Claim 2-9 is cancelled.

Claims 10 and 15 have been amended.

Claims 16-24 have been added.

Claims 1, 10 and 15-24 are currently pending and are under examination.

Claim Rejections - 35 USC 112, first paragraph maintained

4. The rejection of claims 1, 10, 15 and newly added claims 16 -23 under 35 U.S.C. 112, first paragraph scope of enablement maintained as set forth in the previous office action.

The specification, while being enabling for a purified polypeptide having PMK activity comprising the amino acid sequence, SEQ. ID. NO: 7, said purified polypeptide is encoded by the nucleic acid sequence SEQ.ID.NO: 6, a method to identify compounds that inhibit PMK activity of C.albicans, said method comprising contacting the test compound and the polypeptide SEQ.ID.NO: 7 and a diagnostic kit for detecting C.albicans comprising antibodies that specifically binding to the polypeptide SEQ.ID.NO: 7 does not reasonably provide enablement for (1) a purified peptide comprising a sequence possessing at least 90% and 95%-99% identity or a naturally occurring variant, a method to identify compounds that inhibit phosphomevalonate kinase (PMK) activity comprising contacting test compound with said sequence possessing at least 90% identity and (4) a diagnostic kit for detecting the presence of C.albicans comprising antibodies capable of binding to a sequence possessing at least 90% identity . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses an isolated polynucleotide sequence, SEQ.ID.NO: 6, phosphomevalonate kinase (PMK) that is described as ERG 8 gene from C.albicans and its encoding polypeptide, SEQ ID NO: 7. However, it fails to disclose a sequence possessing at least 90%, 95%-99% %identity to SEQ.ID.NO: 7 or a naturally occurring variant. The instant claims comprising a sequence 90%, 95%-99% %identity to SEQ.ID.NO: 7 or a naturally occurring variant identity are not predicted because a purified polypeptide comprising an amino acid sequence (two or three amino acids) of SEQ.ID.NO: 7 plus unlimited and unknown amino acids are not disclosed by the present specification. Similarly a nucleic acid molecule that hybridizes under stringent conditions reads on any 10-30 nucleic acids of SEQ.ID.NO: 6, however, such nucleic acid molecule would not encode the amino acid sequence of SEQ.ID.NO: 7. Thus, the specification provides guidance and direction with regard to a purified polypeptide SEQ.ID.NO: 7. However, there is no guidance or directions on how to make and how to use a polypeptide comprising a sequence 90%, 95%-99% identity to SEQ.ID.NO: 7 and a purified polypeptide encoded by a nucleic acid molecule that hybridizes under stringent conditions to nucleic acids of SEQ.ID.NO: 6. It is known in the art that deletions, or modifications of the amino acids of a protein alter the function of the protein. The amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (Bowie et al. Science, Vol. 247: 1990; p. 1306; p. 1308) and is well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in protein and the result of such modifications is unpredictable based on the instant disclosure.

The specification does not support the broad scope of the claims which encompass a nucleic acid molecule encodes a fragment which can be predictably modified and which regions are critical; what variants, if any, can be made which retain the biological activity of the intact protein; and the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. Further, Houghten et al. (Vaccines, 1986, Edited by Fred Brown: Cold Spring Harbor Laboratory) teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore affect antibody production (p. 21) as well as antibody binding. Houghten et al. also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." And "a protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al. teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the derivatives that retain immunodominant regions and immunological activity if the regions have been altered. The specification teaches that specific primer or probes are required to amplify the PMK gene that encodes the polypeptide or its use

in diagnostic for C.albicans. Therefore, any fragment or variant would not work in diagnostic kit for C.albicans or a method to identify compounds that inhibit PMK activity of the polypeptide.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed polypeptide i.e., fragment with 90%, 95%-99% or in a diagnostic kit in a manner reasonably correlated with the scope of the claims broadly including any as presently claimed. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the protein renders activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed peptide, for the reasons discussed the claims would still expectedly encompass significant changes, which could not be distinguished without undue experimentation. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

Applicants' arguments filed on 11/19/04 have been fully considered but they are not deemed to be persuasive.

Applicant states that in light of the declaration provided by Dr. John Rosamond the rejection should be withdrawn. Further applicant states that claim 1 has been amended to cover polypeptides having PMK activity comprising the amino acid sequence depicted in SEQ.ID.NO: 7 and a sequence possessing at least 90%identity to SEQ.ID.NO: 7 and accordingly variants that retain PMK function as now claimed are enabled. Therefore, such variants may be used in diagnostic kits to identify compounds that inhibit PMK activity.

The examiner acknowledges the Declaration provided by Dr. John Rosamond and attached articles. The examiner reviewed all the documents (including the published papers and Figure 1 of sequence alignment with Saccharomyces cerevisiae) submitted carefully. While the examiner respects the inventor's research experiences in Candida albicans and other microbial molecular biology, the declaration or the articles do not provide any evidence that the claimed polypeptide variants after changes have been made retain phosphomevalonate kinase (PMK) activity. Therefore, to obtain a functional variant having a sequence identity to

SEQ.ID.NO: 7 is left for experimentation because the specification does not support the broad scope of the claims, which encompass modifications.

Applicants further argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because the specification teaches the complete nucleotide and amino acid sequences of the phosphomevalonate kinase (PMK) of SEQ ID NO: 7, protocols for using the DNA of SEQ ID NO: 6 as a probe, and a protocols for testing for enzymatic activity, thermostability, and pH optima and methods for producing variants of a disclosed sequence are within the skill of the ordinary artisan.

This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., encoding a phosphomevalonate kinase (PMK) requires that one of [illegible] skill in the art know or be provided with guidance for the selection of which of the variants have the claimed property. Without such guidance one of [illegible] skill would be reduced to the necessity of producing and testing all of the variants. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting phosphomevalonate kinase (PMK) activity and thermostability; (B) the general tolerance of phosphomevalonate kinase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any phosphomevalonate kinase residues with an expectation of obtaining the desired biological

function; and (D) the specification provides insufficient guidance as to which of the possible choices is likely to be successful.

Applicant seems to agree with the examiner that mutation of a single amino acid may eliminate antigen recognition by a single antibody and yet states that many proteins exist that include substitution, mutation etc. Applicant states that the specification on pages 8 and 11 describe mutations may be introduced into a polynucleotide sequence by site directed mutagenesis and numerous ways to screen for PMK activity to make and use the claimed invention. It is the position of the examiner that while general methods of site directed mutagenesis and numerous ways to screen for PMK activity are known, the specification lacks support for a sequence that has 90 % identity to SEQ.ID.NO: 7 that can be predictably modified and which regions are critical; what variant, if any, can be made which retain the biological activity of the intact protein and the specification provide essentially no guidance as to which screening assay for PMK is likely to be successful and which antibody recognizes this altered polypeptide and thus diagnose the presence of Candida albicans. Further, the claims 1 and 10 are not limited to ERG8 polypeptide from C.albicans having enzymatic activity. Further, claim 10 is not limited to the assays described in the specification because how a test compound inhibits the PMK activity of the claimed polypeptide in the absence of a substrate is not clear. It is concluded that the specification as filed is not enabling for the claimed invention as filed and an artisan would not have been able to practice the invention without undue experimentation. Therefore, limitation of the scope of the invention to an isolated and purified polypeptide from *C.albicans* having PMK activity comprising the amino acid sequence depicted in SEQ.ID.NO: 7 is proper.

Claim Rejections - 35 USC 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The transitional limitation "comprises" similar to the limitations, such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Molecular Research Corp. v. CBS, Inc., 793 F2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App.1948)* ("comprising" leaves "the claim open. for the inclusion of unspecified ingredients even in major amounts". On the other hand, the limitation "consisting of represents closed claim language and excludes any element, step, or ingredient not specified in the claim. In *re Gray, 53 F. 2d 520, II USPQ 255 (CCPA 1931); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948).*

6. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Tsay et al Accession Number: M63648, Mol. Cell. Biol. 11 (2), 620-631 (1991).

Claims are drawn to a purified polypeptide encoded by a nucleic acid molecule that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO: 6 and which nucleic acid molecule encodes a polypeptide having phosphomevalonate kinase (PMK) activity.

Tsay et al disclose a purified 48-kDa size peptide (i. e, 424-amino-acid ERG8 protein) having phosphomevalonate kinase activity encoded by a nucleic acid (see the sequence alignment Qy is the nucleic acid sequence SEQ.ID.NO: 6 that encodes the claimed protein with the Db nucleic acid) that hybridizes with the nucleic acid sequence SEQ.ID.NO: 6 because the nucleic acid sequence matches (see the high lighted first line) at several places with the claimed nucleic acid that encodes a polypeptide. Soluble protein with the predicted 48-kD for phosphomevalonate kinase was also disclosed (see abstract of the article). As very few nucleic

acid molecules are needed for hybridization the disclosed invention reads on the claim 17. Thus the prior art anticipated the claimed invention.

Remarks

7. Claims 1, 10 and 15-23 stand rejected.

Claim 24 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

8. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Respectfully,

Padma Baskar Ph.D.